Iliac vein stenting in postmenopausal leg swelling

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Background: **Leg swelling in menopausal women is well known. Prevailing concept in primary care is that it is polycentric and a treatable cause may not be found. Patients are placed on empiric diuretics often without benefit. Our clinical experience indicates that iliac venous vein obstruction is the core cause; a variety of secondary factors common in postmenopausal women precipitate symptoms.**

Patients and Methods: **A total of 163 limbs in 150 postmenopausal women (≥55 years of age) with leg swelling unresponsive to conservative therapy underwent intravascular ultrasound-guided iliac vein stenting over an 11-year period. Preoperative investigations included duplex, airplethysmography, venous pressure tests, contrast studies, and lymphangiography. The postmenopausal group constituted 9% of all limbs (n = 1760) stented for chronic venous disease (CVD) during the same period and 18% of those stented for swelling (n = 922). Median age was 67 (range, 55-92) and left-to-right ratio 2:1.**

Results: **Iliac vein obstruction was "primary" (nonthrombotic) in 65% and postthrombotic in 35% of limbs; 35% of limbs had obstruction only and 65% combined obstruction/reflux. Lymphatic dysfunction was present in 21% of the limbs. Mean intravascular ultrasound area stenosis was 68% ± 22 SD. Mean follow-up was 22 months (±26 SD) (range, 1-113 months). Secondary stent patency (6 years) was 100% in primary and 91% in postthrombotic limbs; overall 98%. Swelling improved significantly ($P < .0001$) from preoperative grade 2.5 (±0.8 SD) to postoperative grade 1.2 (1.2 SD). Associated pain also improved significantly ($P < .0001$) from preoperative visual analog scale 3.5 (±3 SD) to postoperative 0.9 (2.1 ± SD). Quality-of-life (CIVQ) scores improved significantly in every category and overall ($P < .0001$).**

Conclusions: **Patients with postmenopausal leg swelling often have obstructive venous pathology even though suggestive venous history and other signs are often absent. Morbidity arises from painful swelling that affects mobility, quality of life, and ability of self-care at later stages of life. Outpatient percutaneous iliac vein stenting affords substantial symptom relief and improvement in quality-of-life measures. Recognition of the clinical complex as a distinct entity of venous origin may lead to greater awareness and effective treatment. (J Vasc Surg 2011;53:123-30.)**

Leg swelling in postmenopausal women is a common clinical problem. After systemic causes have been excluded, there is a large segment where a specific cause is not apparent. Hormonal changes that occur with aging and menopause appear to have a role, but the precise mechanisms remain ill-defined.[1-3] Since prior history or features of chronic venous disease (CVD) is usually absent, a venous cause is seldom investigated. Although other menopausal symptoms may be present,[1,4] the leg swelling is a dominant feature in many patients seeking specific treatment. When the edema is substantial or when associated with pain, quality of life (QOL) may be impacted in a significant way (Figs 1 and 2). In geriatric women, the condition may be disabling, hindering ability of self-care prompting considerations of assisted living. The condition, although frequently treated in clinical practice, is yet to be defined as a specific clinical entity. A search of the Pubmed and MeSh databases returns no specific subheading, only links to related features such as hormones or edema. This article details our clinical experience with this condition. A venous basis was found to underlie the leg swelling and venous stenting may afford relief. Based on the unique clinical features and possible corrective treatment, it is argued that the symptom complex be recognized as a specific clinical entity with venous etiology.

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PATIENTS AND METHODS

A total of 163 limbs in 150 postmenopausal women (≥55 years age) presenting with leg swelling as the primary complaint and unresponsive to conservative therapy underwent intravascular ultrasound (IVUS)-guided iliac vein stenting over an 11-year period. The age (≥55) selection to define the postmenopausal group was based on the average age of menopause in United States (±52 years) per National Institutes of Health. Bilateral leg swelling was present in 20 (13%) patients and bilateral venous stenting was carried out in 13 (9%) of the patients. The postmenopausal group constituted 9% of all CVD limbs (n = 1760) stented during the same period and 18% (n = 922) of those stented for swelling. Patients with chronic venous disease or proximate history of deep venous thrombosis (DVT) (≤5 years) preceding onset of symptoms were excluded to refine the subset without other well-known venous causes of similar symptomatology. Patients with a remote (>5 years) history of DVT were, however, included in analysis, as it is often not considered by primary physicians when

Fig 1. Painful foot swelling with inability to wear proper footwear.

Fig 2. Limb swelling in a postmenopausal woman retarding mobility; note compression marks.

encountering postmenopausal leg swelling. Median age was 68 (range, 55-92) and left-to-right ratio 2:1.

Investigations. A comprehensive set of laboratory and radiologic investigations were carried out. This included arm/foot pressure differential, ambulatory venous pressure, air plethysmography, duplex examination, isotope lymphangiography, and transfemoral venography with exercise femoral pressure measurement. Test details have been described before.[5] Since one or more tests were not carried out for technical or patient compliance reasons in individual patients, n values for cited results vary and are noted in context. IVUS examination of the iliac outflow was the final arbiter of stenosis; stents were concurrently placed with prior consent.

Technique. The technique of iliac venous stenting has been described in detail before.[5-10] Briefly, large (14-18 mm diameter) Walstents (Boston Scientific Corporation, Inc, Natick, Mass) were placed with generous overlap at stent joins after predilatation to normal vein caliber for the location. Stents extended from the distal inferior vena cava to a landing site free of disease below, often the common femoral vein below the inguinal ligament. Concurrent laser saphenous vein ablation[6] was carried out in 20 limbs (13%), as saphenous reflux was thought to be contributory but not the main cause of the leg swelling. Nonocclusive lesions were stented in 159 limbs (98%), and recanalization of chronic total occlusions[9] was required in four limbs (2%).

Perioperative low-molecular-weight heparin and intraoperative heparin (100 U/kg) or bivalrudin (50 mg) were used. Patients were discharged after overnight stay on long-term aspirin unless specific thrombophilia or extensive postthrombotic disease was present, in which case warfarin was used.

Patients were clinically examined at 6 weeks, 3 months, 9 months, and then annually. The CIVIQ method was used for QOL assessment;[11] latest patient response was used for analysis. Stent patency was established by venography at 3 to 6 months and yearly thereafter. Duplex ultrasound scanning[12] has been used in the last few years in addition, for more frequent stent surveillance than is possible with venography.

Data analysis. Data were extracted from electronic medical records that were contemporaneously created during clinical evaluation. Continuous and categorical variables were analyzed by paired (two-tailed) nonparametric Wilcoxon-rank test and χ^2 test, respectively. Secondary patency rates and clinical outcomes were calculated using cumulative analysis with the Kaplan-Meier method. These curves were pruned at SEM > 10%. A commercially available statistical program (Graph Pad Prism for Windows [version 3.0]) was used for analysis. A *P* value of less than .05 was considered significant.

RESULTS

Clinical features. All limbs were categorized as class C_3 (CEAP). The mean duration of leg swelling was 25 ± 40 months before referral. Limb swelling was assessed preoperatively by physical examination (grade 1, pitting edema; grade 2, ankle edema; grade 3, gross; involving the leg or limb) assigning the highest grade of swelling present. Distribution of swelling grades 1 to 3 in analyzed limbs was 23%, 15%, and 62% respectively. Mean grade of swelling was 2.5 ± 0.8 SD. Limb pain was assessed by visual analogue scale as described by Scott.[13] Associated pain was

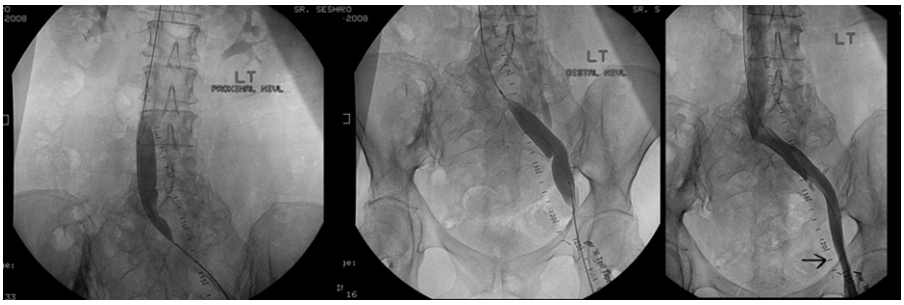

Fig 3. Nonthrombotic iliac vein lesion (NIVL) in a patient with postmenopausal leg swelling. Both proximal and distal lesions are present (*left and middle*). The venogram was unremarkable (*right*). Diagnostic sensitivity of venography in the diagnosis of iliac vein lesions is poor (*see text*).

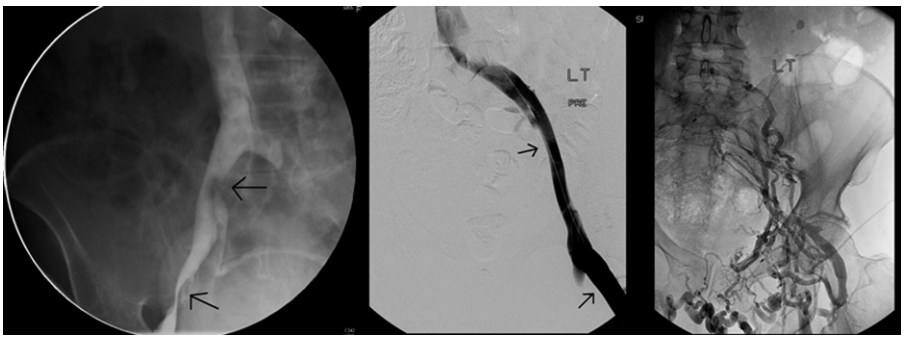

Fig 4. Types of postthrombotic iliac vein lesions that can remain silent for years before swelling is precipitated by a secondary insult. Focal stenosis (*left*); diffuse iliac stenosis (*center*); note size discrepancy between the femoral and iliac veins (*arrows*) and the absence of collaterals; chronic total occlusion (*right*).

Table I. Clinical history

Remote events (n = 150 patients)	
DVT/phlebitis:	20 (13%)
Trauma/major surgery:	48 (32%)
Cancer/radiation:	13 (9%)
Congestive heart failure:	4 (3%)
Cellulitis:	2 (1%)
Medications (n = 150 patients)	
Hormone replacement:	46 (31%)
Cardiac/antihypertensive:	91 (61%)
Diuretics:	65 (43%)
Recent events precipitating leg swelling (n = 163 limbs)	
Trauma/major surgery:	44 (27%)
Immobility/obesity:	10 (6%)
Cellulitis:	10 (6%)
Cancer/radiation:	2 (1%)

DVT, Deep venous thrombosis.

present in 114 (70%) and absent in 49 (30%) limbs. Mean pain level on visual analog scale (VAS) was 3.5 ± 3.0 SD.

The etiology of iliac vein stenosis was primary in 106 (65%) (Fig 3) and postthrombotic in 57 (35%) limbs (Fig 4). A remote history of previous DVT, (often forgotten) was elicited in 20 (13%) patients; 5 or more years had elapsed before onset of current symptoms (Table I). A previous history of prothrombotic events (trauma, major surgery, cancer, congestive failure, and cellulitis) without a clear history of DVT was elicited in 45% of patients. Nearly two-thirds of patients were on cardiovascular medications known to promote limb swelling and nearly one-third of patients were receiving hormone replacement therapy. About half the patients had been placed on empiric diuretics. Symptoms were precipitated by recent trauma/orthopedic surgery in 27% of limbs. New onset of reflux in the context of a preexisting iliac vein obstruction could have been a precipitating cause in others. Reflux details are given below.

Mean IVUS area stenosis (electronic planimetry, poststent area minus prestent area as ratio at maximum point of stenosis) was 68% ± 22 SD. In 21 limbs, the IVUS calculated area stenosis was <50%. In 9/21 of these limbs, IVUS area stenosis was <50% but had failed to detect a higher-grade distal nonthrombotic iliac vein lesion (NIVL) stenosis near the hypogastric orifice, which was unmasked by gentle balloon "sizing" (≤1 atm inflation).[10] In the remaining 12 limbs, the poststent area had residual stenosis from continuing compression of the stent by the lesion[10] despite pre- and poststent dilatation. Because of the way area stenosis was calculated, this resulted in an underestimation of the true stenosis present. When the poststent area was normalized by substituting luminal area values found in

Table II. Reflux detail in 163 limbs stented for obstruction

Type of reflux	*Limbs*	*Prevalence (%)*
No venous reflux	57	35%
Superficial reflux	51	31%
Deep reflux alone	17	10%
Deep + superficial reflux	32	20%
Data missing	6	4%

Table III. Severity of reflux (n = 100 limbs)[a]

	Limbs	*Percent*
Reflux multisegment score[b]		
< 3:	77	77%
≥ 3:	23	23%
Axial reflux	7	7%
	Limbs	*Median ± SD*
AVP, percent drop	69	70% ± 18
AVP; VFT, seconds	68	42 ± 31
APG: VFI_{90}, mL/s	84	1.6 ± 1.4

APG, Air plethysmography; *AVP,* ambulatory venous pressure; *VFI_{90},* venous filling index. *VFT,* venous refilling time.
[a]Fifty-seven limbs with no reflux and 6 others with missing data were excluded from the total number of limbs (n = 163).
[b]A score of 1 each is given to reflux in the above-knee great saphenous vein (GSV), below-the-knee GSV, small saphenous vein, perforators, femoral vein, profunda femoris, and popliteal vein. The total reflux score for the limb is calculated (max 7).

normal adults,[9,10] the stenosis was >50% in all of the latter limbs.

In 57 limbs (35%), iliac vein obstruction was the only pathology and there was no associated reflux (Table II). In the remainder, obstruction was associated with reflux as follows: superficial reflux only in 51 (31%) limbs, deep reflux only in 17 (10%) limbs, and combination in 32 (20%) limbs. The deep reflux was segmental in 42/49 (84%) of limbs with deep reflux. Perforator reflux was present in 10 limbs (1%). The severity of associated reflux as judged by several parameters (Table III) was mild. Only 23 limbs had a multisegment score of ≥3 and axial reflux was present in only seven limbs. Values for ambulatory venous pressure and VFI_{90} in limbs with reflux were within the range considered "normal" (Normal values for ambulatory pressure drop ≥50%, VFT 20 s and VFI_{90} 2 mL/s).

Lymphangiography was normal in 92 (79%) of 114 limbs with available data; abnormalities were present in 22 (21%) limbs: delayed 15 (14%) and absent in 6 (6%) limbs and enhanced in 1 limb (1%). Preoperative test parameters suggestive of venous obstruction are detailed in Table IV. One or more preoperative tests were suggestive of obstruction in 130 limbs (80%) and were unrevealing in 33 limbs (20%), although stentable obstructions were found with IVUS in all during the procedure. Thirty-day mortality was nil. DVT occurred in three limbs <30 days and in four others later (overall 4%).

Table IV. Tests suggestive of venous obstruction in limbs before stent placement

	Positive/tested limbs	*Sensitivity %*
Venography:		
Lesions suspected[a]	85/124	69%
Collaterals	32/116	28%
Femoral vein pressures:		
≥3 mmHg gradient over contralateral limb	10/96	10%
≥4 mmHg increase with exercise	37/111	33%
Arm/foot pressure difference ≥4 mmHg rest	7/90	8%
Reactive hyperemia ≥6 mm Hg at rest	44/90	49%
Duplex: lack of phasicity	54/136	40%

One or more tests suggested obstruction in 80% of limbs; in 20% of limbs, none of the tests were positive. IVUS confirmed lesions in all 163 limbs.
[a]Interpretation by authors with bias.

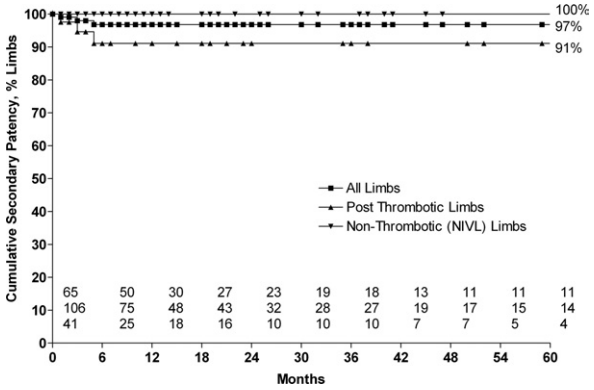

Fig 5. Cumulative stent patency (*secondary*) curves in postmenopausal leg swelling. Separate curves are shown for primary (*NIVL*), postthrombotic etiologies, and overall.

Stent outcome. Cumulative patency and cumulative relief of pain and swelling is shown in Figures 5, 6 and 7, respectively. Secondary stent patency (6 years) was 100% in primary and 91% in postthrombotic limbs; overall 98%. Four stents occluded during the observation period and three were reopened by catheter lysis. There was significant improvement in swelling after stent correction (poststent swelling 1.2 ± 1.2 SD, $P < .0001$) and in pain (poststent VAS 0.9 ± 2.1 SD, $P < .0001$). QOL (CIVIC) outcome is shown in Table V. There was significant improvement in all six categories and in the aggregate score.

DISCUSSION

Currently, when a postmenopausal woman presents with leg swelling to the primary physician, duplex examination for DVT is commonly carried out. If negative, additional investigations necessary to rule out cardiac, renal, autoimmune, and other systemic causes may be carried out as well. When these causes are ruled out, an amorphous polycentric etiology is assigned and the condition is treated

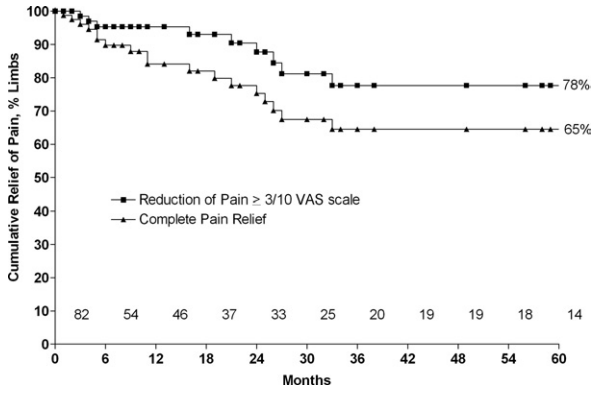

Fig 6. Cumulative relief of pain after iliac vein stent placement in patients with postmenopausal leg swelling. Separate curves are shown for significant (≥ *3 VAS*) and total relief of pain.

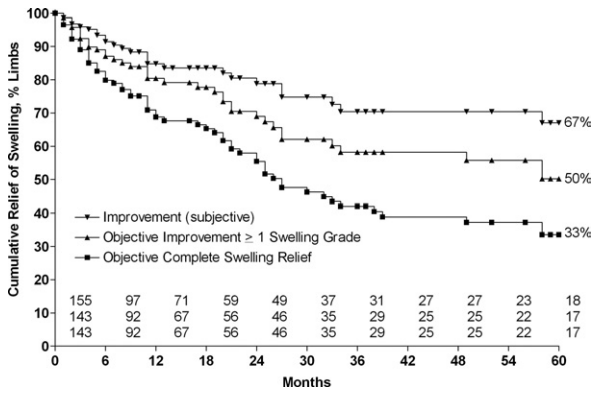

Fig 7. Cumulative relief of swelling after iliac vein stent placement in postmenopausal women. The upper curve shows swelling improvement as reported by the patient (*subjective*). The bottom two curves represent objective assessment by examination: significant (≥*1 grade*) improvement and for complete relief of swelling.

Table V. Quality of life (CIVIQ) before and after stent placement in postmenopausal leg swelling (n = 65 patients[b])

CIVIQ categories	*Prestent score*	*Poststent score*	P *value*
Pain	4 (1-5)	3 (1-5)	.0007[a]
Work	4 (1-5)	3 (1-5)	.0004[a]
Sleep	4 (1-5)	2 (1-5)	.0044[a]
Social	4 (1-5)	3 (1-5)	.0055[a]
Morale	3 (1-5)	3 (1-5)	.002[a]
Total	71 (20-100)	50 (20-96)	<.0001[a]

[a]Significant.
[b]Data available with both prestent and poststent questionnaires.

empirically with diuretics (seldom effective in regional edema) and compression. As history and other signs suggestive of CVD are usually absent, relevant venous investigations are seldom carried out especially when bilateral leg swelling is present. When accompanied by other menopausal symptoms such as for example "hot flashes", hormonal supplements may be prescribed.[1,4] Amelioration of edema with hormonal supplements has been variable. It seems unlikely that this approach will be useful except in the mildest forms of leg swelling. Many patients in this age group are on cardiac and antihypertensive medications, some of which are known to promote leg swelling. Switchover to alternates without this side effect when feasible (frequently not) may occasionally be rewarding. As outlined in this article, an underlying significant iliac vein obstruction is present in those presenting with highly symptomatic postmenopausal leg swelling. Significant bilateral lesions are present in about 20% of patients with iliac vein obstruction.[5,14] Compression when properly applied can be effective but fails for a variety of reasons.[15]

In a fraction of the patients, a remote history of thrombosis years or decades ago may be elicited on specific questioning. In others, a prothrombotic event such as severe trauma, fracture and immobilization, past use of birth control pills, major surgery, or illness can be elicited. A fraction of all DVT, perhaps about 30%, is estimated to be silent. Also likely, some thromboses, particularly of the iliac vein were simply missed. Examination of the iliac vein is not routine in many laboratories. The incidence of DVT increases with age.[16,17] Based on estimated annual incidence, 15% to 20% of postmenopausal women are likely to harbor postthrombotic limbs. The iliac vein pathology was postthrombotic in one-third of the cases and was primary (NIVL) in the other two-thirds in this analysis. These are clearly long-standing lesions that predated the onset of leg swelling. A previously silent lesion had become symptomatic for some reason. We hypothesize that iliac vein lesions are permissive, remaining silent until additional insult to the limb precipitates symptoms.[18] Many human disease conditions are precipitated by onset of secondary pathology in the context of preexisting silent permissive primary pathology. Some examples include patent foramen ovale/parodoxic embolus, obesity/diabetes, cardiac defects/endocarditis, ureteric reflux/pyelonephritis, hypertension/stroke, and lung cavitation/aspergilloma. Typically, the prevalence of the permissive lesion in the diseased subset is several times higher than in the general population.[19-21] Significant (>50%) NIVL type of lesions in silent form are estimated to be present in about 25% of the general population[22,23] but are found in >90% of symptomatic patients.[18] This report suggests that post-thrombotic iliac vein lesions in addition to NIVLs, can remain silent and function as permissive lesions until secondary pathology precipitates symptoms. Recurrent DVT is a major instigator of postthrombotic syndrome, which implies a similar concept.[24]

Women are prone to numerous other events in the menopausal years that are productive of symptoms in the context of a preexisting permissive iliac vein pathology (Fig 8). These include antihypertensive and cardiac medications that promote fluid retention,[25] joint surgery, saphenous vein harvest for coronary or other bypass, arthritis that retards mobility and calf pump function, a sedentary habit

Fig 8. Trauma to the limb (*left*), infection (*cellulitis, center*), or orthopedic joint replacement (*bilateral knee replacement, right*) can precipitate leg swelling in the context of a preexisting *permissive* iliac vein lesion (*see text*). Postmenopausal women are subject to numerous other secondary factors including onset of reflux that may aggravate to render a previously silent iliac vein obstructive lesion symptomatic with onset of leg swelling.

increasing with age or obesity resulting in prolonged seated orthostasis (TV leg), postmenopausal hormonal changes, and onset of reflux, incidence of which increases with age[26] and has a higher prevalence in women. The secondary insult may not be productive of leg swelling in the absence of venous pathology. For example, saphenous reflux, in and of itself seldom produces grade 3 limb swelling, although lesser-grade swelling may be seen. Similar comments apply to nonaxial segmental reflux when the reflux score is low ($\leq$2) or when ambulatory venous pressure or airplethysmography (VFI_{90}) do not indicate severe global reflux as was the case in this case material. Onset of cellulitis can further destabilize fluid homeostasis and produce lymphatic damage. Secondary lymphatic dysfunction is a feature of venous disease.[27,28] Iliac vein stenting alone has been shown to be effective in symptom relief in many of these instances even when the specific secondary pathology (recurrent cellulitis, secondary lymphedema, and reflux even if severe) is not directly addressed.[29-31]

A general observation in managing disease with complex permissive/secondary pathologies is that correction of the permissive pathology alone is often sufficient to ameliorate symptoms and the need for specific correction of secondary pathology is lessened. For example, weight reduction alone may control secondary diabetes; elimination of acid reflux often remits night time asthma and so on. The results of stenting to correct the underlying iliac vein stenosis may be viewed in this fashion.

Patients reported swelling improvement in 67% of limbs. This could be confirmed by objective examination in 50% (cumulative) of the limbs where swelling had improved by $\geq$1 grade with complete absence of swelling noted in 33% of the stented limbs at 5 years. The discrepancy may be due to placebo effect or swelling is perceived to be less because it is less painful. However, the swelling assessment methodology itself understates clinical relief. For example, swelling of the entire limb may recede below the knee; and massive leg swelling that has visibly improved by 50% or more will show no grade change (grade 3) after stent placement in either instance although affording easier mobility. Similarly, massive foot swelling may improve enough (still grade 2) to allow shoe wear. The grading system used herein predates the VCSS[32] system and was retained because the latter is entirely subjective. Limb swelling is perhaps the most recalcitrant among CVD manifestations and relatively difficult to eradicate completely because fluid homeostasis even in normal individuals is so precarious.[33-36] Identifying and correcting stent malfunctions in patients with symptomatic residual/recurrent swelling may improve outcome.[10] Preexisting reflux does not worsen after stent placement.[5]

Residual swelling is better tolerated if the associated pain is relieved. A percentage (78%) (cumulative) of limbs in this series had substantial pain relief with total relief in 65% at 5 years after the stent procedure.

Clinical outcome is probably better reflected in QOL measures, which showed significant improvement in every category. QOL methodology used in this study is free of author bias in assessment, as it depends solely on patient responses.

Underlying venous pathology in postmenopausal leg swelling is not different from that in other subsets, but hormonal influences probably play a secondary precipitating role. These patients tend not to be appropriately investigated because of presentation of swelling sans other venous signs. The belief that "fluid retention" is characteristic of this stage in life is pervasive. Venous investigations should be pursued in postmenopausal leg swelling unresponsive to conservative measures. Traditional venous investigations, such as routine duplex or venography (Fig 3) are unsatisfactory for assessment of iliac vein pathology.[29] Venographic collaterals are infrequently present. Other signs pointing to the presence of an obstructive lesion are often subtle and easily missed on routine interpretations. Nearly one-third of the lesions were impervious to even sensitized observers as in this report. Diagnostic yield may

be improved by employing a panoply of other tests (Table IV), but this is unlikely to be adopted in routine practice. In contrast, IVUS has a very high diagnostic yield[18,37] and is recommended even if traditional investigations are negative. IVUS is conveniently combined with iliac vein stenting (with prior consent), as it is essential to successful stent placement. About 10% of significant lesions are impervious even to IVUS, and routine "balloon sizing" of the entire iliac-femoral segment is recommended to unmask hidden lesions.[10] The degree of stenosis suitable for stenting remains unsettled. The idea of "critical" stenosis is derived from the arterial system where a stenotic lesion produces a flow reduction in the context of arteriolar resistance. In the venous system, a tandem distal functional stenosis represented by resistance arterioles does not exist and the aim is to reduce pressure at the venular end of the capillary to improve fluid homeostasis. In practice, we have found correction of ≥50% IVUS area stenosis to yield clinical relief.[5]

Stenting of IVUS-identified lesions is minimally invasive, safe, has excellent long-term patency, and affords substantial symptom relief and improved QOL in patients with postmenopausal leg swelling.

AUTHOR CONTRIBUTIONS

Conception and design: SR, PN
Analysis and interpretation: SR, PN
Data collection: SR, MO, PN
Writing the article: SR, PN
Critical revision of the article: SR, PN
Final approval of the article: SR, PN
Statistical analysis: SR, MO, PN
Obtained funding: Not applicable
Overall responsibility: SR

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